U.S. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs During Pregnancy for Maternal Health and Reduction of Perinatal Transmission of Human Immunodeficiency Virus Type 1 in the United States

SUMMARY

These recommendations update the 1994 guidelines developed by the U.S. Public Health Service for use of zidovudine (ZDV) to reduce the risk of perinatal human immunodeficiency virus (HIV) type 1 transmission.[1]*(MMWR 1994) In February 1994, the results of Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 demonstrated that ZDV chemoprophylaxis could reduce perinatal HIV-1 transmission by nearly 70%.(Connor 1994) Since that time, epidemiologic data have confirmed the efficacy of ZDV for reduction of perinatal transmission and extended this efficacy to children of women with advanced disease, low CD4 lymphocyte count and prior ZDV therapy. Additionally, there have been major advances in understanding the pathogenesis of HIV-1 infection and in the treatment and monitoring of HIV-1 disease. These advances have resulted in changes in standard antiretroviral therapy recommendations for HIV-1-infected adults in the United States to more aggressive combination drug regimens that maximally suppress viral replication. Although considerations related to pregnancy may factor into decisions as to timing and choice of therapy, pregnancy per se is not an adequate reason to defer standard therapy. There are unique considerations regarding use of antiretroviral drugs in pregnancy, including the potential need to alter dosing due to physiologic changes associated with pregnancy, the potential for adverse short- or long-term effects on the fetus and newborn, and effectiveness for reducing the risk of perinatal transmission. Data to address many of these considerations are not yet available. Therefore, offering antiretroviral therapy to an HIV-1-infected woman during pregnancy, whether primarily to treat her HIV-1 infection, primarily to reduce perinatal transmission, or for both purposes, should be accompanied by a discussion of the known and unknown short- and long-term benefits and risks of such therapy for her and her infant. Standard antiretroviral therapy should be discussed with and offered to HIV-1-infected pregnant women. Additionally, to prevent perinatal transmission, ZDV chemoprophylaxis should be incorporated into whatever antiretroviral regimen is offered. This document is intended to give the health care professional information for discussion with the woman to enable her to make an informed decision regarding use of antiretroviral drugs during pregnancy.*

[1] Information included in these guidelines may not represent FDA approval or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

INTRODUCTION

In February 1994, PACTG Protocol 076 demonstrated that a 3-part regimen of ZDV could reduce the risk of mother to child HIV-1 transmission by nearly 70%.(Connor 1994) The regimen includes oral ZDV initiated at 14 to 34 weeks gestation and continuing throughout pregnancy, followed by intravenous ZDV during labor and oral administration of ZDV to the infant for 6 weeks after delivery (Table 1). In August 1994, a U.S. Public Health Service (USPHS) Task Force issued recommendations for use of ZDV for reduction of perinatal HIV-1 transmission (MMWR 1994), and in July 1995, the USPHS issued recommendations for universal prenatal HIV-1 counseling and HIV-1 testing with consent for all pregnant women in the U.S.(MMWR 1995) In the three years since these results became available, epidemiologic studies in the U.S. and France have demonstrated dramatic decreases in perinatal transmission following incorporation of the PACTG 076 ZDV regimen into general clinical practice.(Cooper 1996; Fiscus 1996; Fiscus 1997; Thomas 1997; Blanche 1997; Simonds 1996)

Since 1994 there have been major advances in understanding the pathogenesis of HIV-1 infection and in the treatment and monitoring of HIV-1 disease. It is now appreciated that the rapidity and magnitude of viral turnover during all stages of HIV-1 infection is much greater than previously recognized; plasma virions are estimated to have a mean half-life of only 6 hours.(Perelson 1996) Thus, current therapeutic interventions focus on early initiation of aggressive combination antiretroviral regimens to maximally suppress viral replication, preserve immune function, and reduce the development of resistance.(Havlir 1996) New, potent antiretroviral drugs which inhibit the protease enzyme of HIV-1 are now available. When a protease inhibitor is used in combination with nucleoside analogue reverse transcriptase inhibitors, plasma HIV-1 RNA levels may be reduced for prolonged periods of time to undetectable levels using current assays. Improved clinical outcome and survival have been observed in adults receiving such regimens.(Hammer 1997, Gulick 1997) Additionally, more direct quantitation of viral load has become available through assays that measure HIV-1 RNA copy number; these assays have provided powerful new tools to assess disease stage and risk for progression as well as the effects of therapy. These advances have led to major changes in the standard of care of treatment and monitoring for HIV-1-infected adults in the U.S..(PanelRec 1997).

There have also been advances in the understanding of the pathogenesis of perinatal HIV-1 transmission. It is now recognized that the majority of perinatal transmission likely occurs near to or during delivery.(Mofenson 1997) Additional data and follow-up are now available on infants and women enrolled in PACTG 076 demonstrating the short-term safety of the ZDV regimen, but new data from animal studies on the potential for transplacental carcinogenicity of ZDV affirm the need for long-term follow-up of children with antiretroviral exposure *in utero*.(Olivero 97)

These developments have important implications for maternal and fetal health. Antiretroviral use in HIV-1 infected women during pregnancy must take into account two separate but related issues: 1) antiretroviral treatment of the woman's HIV infection, and 2) antiretroviral chemoprophylaxis to reduce the risk of perinatal HIV-1 transmission. The benefits of antiretroviral therapy in the pregnant woman must be weighed against the risk of adverse events in the woman, fetus and newborn infant. While ZDV chemoprophylaxis alone has been shown to significantly reduce the risk of perinatal transmission, antiretroviral monotherapy is now considered to be suboptimal for treatment of HIV infection, and combination drug therapy is the current standard of care when considering treatment of the woman's HIV infection in the U.S.

Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents, including use of antiretroviral drugs for treatment of infected women who are pregnant, have been published by the USPHS.(Panel 1997) The current document will focus on antiretroviral chemoprophylaxis for reduction of perinatal transmission, and will review the special considerations regarding use of antiretroviral drugs in pregnant women; update the results of PACTG 076 and related clinical trials and epidemiologic studies; discuss use of HIV-1 RNA assays during pregnancy; and provide updated recommendations on antiretroviral chemoprophylaxis for the reduction of perinatal transmission.

These recommendations have been developed for use in the United States. Although perinatal HIV-1 transmission is an international problem, alternative strategies may be appropriate in other countries. The policy and practices in other countries regarding use of antiretroviral drugs for reduction of perinatal HIV-1 transmission may differ from these recommendations, and will depend on local considerations, including availability and cost of ZDV, access to facilities for safe intravenous infusions during labor, and alternative interventions that may be under evaluation in that area.

SPECIAL CONSIDERATIONS REGARDING THE USE OF ANTIRETROVIRAL DRUGS BY HIV-1-INFECTED PREGNANT WOMEN AND THEIR INFANTS

Treatment recommendations for HIV-1-infected pregnant women have been based on the belief that therapies of known benefit to women should not be withheld during pregnancy unless there are known adverse effects on the mother, fetus or infant and these adverse effects outweigh the benefit to the woman.(Minkoff 1997) The Panel on Clinical Practices for Treatment of HIV Infection recommends that guidelines for optimal antiretroviral therapy in pregnant HIV-infected women should be the same as delineated for non-pregnant adults.(Panelrec 1997) However, it must be realized that the potential impact of such therapy on the fetus and infant is unknown, and long-term follow-up is needed for children who have had exposure to antiretroviral drugs *in utero*. The decision to use any antiretroviral drug during pregnancy should be made by the woman following discussion with her health care provider regarding the known and unknown benefits and risks to her and her fetus.

Combination antiretroviral therapy, generally consisting of two nucleoside analogue reverse transcriptase inhibitors and a protease inhibitor, is the currently recommended standard treatment for non-pregnant HIV-1-infected adults.(Panel 1997) Pregnancy *per se* should not preclude use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of infected pregnant women are subject to unique considerations, including potential changes in dosing requirements due to the physiologic changes associated with pregnancy and the potential effects of the antiretroviral drug on the fetus and newborn.

Physiologic changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, biotransformation and elimination in the pregnant woman, thereby affecting drug dose requirements. During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase over gestation accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and there are changes in metabolic enzyme pathways in the liver. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, and biotransformation of drugs by the fetus and placenta as well as elimination of drugs by the fetus can also affect drug pharmacokinetics in the pregnant woman. Additional important considerations regarding drug use in pregnancy are the effects of the drug on the fetus and newborn, including the potential for teratogenicity, mutagenicity, or carcinogenicity, and the pharmacokinetics and toxicity of transplacentally transferred drugs. The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself, but the dose ingested, the gestational age at exposure, duration of exposure, the interaction with other agents to which the fetus is exposed, and to an unknown extent, the genetic makeup of the mother and fetus.

Information about the safety of drugs in pregnancy comes from animal toxicity data, anecdotal experience, registry data and clinical trials. There are currently minimal data available on the pharmacokinetics and safety of antiretrovirals during pregnancy for antiretrovirals other than ZDV. In the absence of data, drug choice needs to be individualized based on discussion with the woman and available data from preclinical and clinical testing of the individual drugs.

Preclinical data include *in vitro* and animal *in vivo* screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. It is important to recognize that the predictive value of such tests for adverse effects in humans is unknown. For example, of approximately 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans.(Mills 1995) In addition to antiretroviral agents, many drugs commonly used to treat the consequences of HIV-1 infection may have positive findings on one or more of these screening tests. For example, acyclovir is positive on some *in vitro* carcinogenicity and clastogenicity assays and is associated with some fetal abnormalities in rats; however, data on human experience from the Acyclovir in Pregnancy Registry indicate no increased risk of birth defects in infants with *in utero* exposure to acyclovir to date.(MMWR 1993) Table 2 shows the FDA Pregnancy Category and available data regarding placental passage and long-term animal carcinogenicity studies for currently approved antiretroviral drugs.

Nucleoside Analogue Reverse Transcriptase Inhibitors

Of the five currently approved nucleoside analogue antiretrovirals, only ZDV and lamivudine (3TC) pharmacokinetics have been evaluated in clinical trials in human pregnancy to date. ZDV is well-tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2 mg per kg body weight orally every 6 hours, as observed in PACTG 076. A small phase I study in South Africa evaluated the safety and pharmacokinetics of 3TC alone or in combination with ZDV in 20 infected pregnant women starting at 38 weeks gestation through labor and given for 1 week following birth to their infants.(Johnson 1996, Moodley 1997) The drug was well-tolerated in the women at the recommended adult dose of 150 mg orally twice daily, had pharmacokinetics similar to those observed in non-pregnant adults, and no pharmacokinetic interaction with ZDV was observed. No data are currently available regarding the pharmacokinetics of 3TC administered earlier than 38 weeks gestation. The drug crossed the placenta, achieving comparable serum concentrations in the woman, umbilical cord and neonate, and no short-term adverse effects were observed in the neonates. Oral clearance of 3TC in infants at 1 week of age was prolonged compared to older pediatric populations (0.35 L per kg per hour compared to 0.64-1.1 L per kg per hour, respectively). There are currently no data on 3TC pharmacokinetics between 2-6 weeks of age, and the exact age at which 3TC clearance begins to approximate that in older children is not known. Based on these limited data, 3TC in a dose of 150 mg administered orally twice daily in pregnant HIV-1-infected women and 2 mg per kg body weight administered orally twice daily in their neonates (half the dose recommended for older children) is being evaluated in several phase I studies in combination with ZDV and other drugs in the U.S., and in a phase III perinatal prevention trial in Africa.

In rodent studies, prolonged, continuous high doses of ZDV administered to adult rodents have been associated with the development of noninvasive squamous epithelial vaginal tumors in 3% to 12% of females.(Ayers 1996) In humans, ZDV is extensively metabolized, and the major form of ZDV excreted in the urine is the glucuronide, whereas in mice, high concentrations of unmetabolized ZDV are excreted in the urine. It is hypothesized by scientists at Glaxo-Wellcome, Inc., the manufacturer of ZDV, that the vaginal tumors in mice may be a topical effect of chronic local ZDV exposure of the vaginal epithelium, resulting from reflux of urine containing highly concentrated ZDV from the bladder into the vagina. Consistent with this hypothesis, in a study conducted by Glaxo-Wellcome, Inc. in which 5 or 20 mg ZDV/mL saline was administered intravaginally to female mice, vaginal squamous cell carcinomas were observed in mice receiving the highest concentration.(Ayers 1996) No increase in the incidence of tumors in other organ sites has been seen in other studies of ZDV conducted in adult mice and rats. High doses of zalcitabine (ddC) have been associated with the development of thymic lymphomas in rodents. Long-term animal carcinogenicity screening studies in rodents administered ddI or 3TC are negative; similar studies for stavudine (d4T) have not been completed.

Two rodent studies evaluating the potential for transplacental carcinogenicity of ZDV have had differing results. In one ongoing study carried out by scientists at the National Cancer Institute, two very high daily doses of ZDV were administered during the last third of gestation in mice.(Olivero 1997) The doses chosen for this study were near the maximum dose beyond which lethal fetal toxicity would be observed and approximately 25 and 50 times greater than the daily dose given to humans, although the cumulative dose received by the pregnant mouse was similar to the cumulative dose received by a pregnant woman taking 6 months of ZDV. In the offspring of ZDV-exposed pregnant mice at the highest dose level followed for 12 months, a statistically significant increase in lung, liver, and female reproductive organ tumors were observed; the investigators also documented incorporation of ZDV into the DNA in a variety of newborn mouse tissues, although this did not clearly correlate with the presence of tumors. The second study was carried out by scientists at Glaxo-Wellcome, Inc.. In that study, pregnant mice were given one of several regimens of ZDV; doses were based on pharmacokinetic data in mice and humans and were intended to achieve blood levels somewhat higher (approximately 3-fold) than those achieved in clinical practice. The daily doses received by mice during gestation ranged from one-twelfth to one-fiftieth the daily doses received by mice in the previous study. Some of the offspring also received ZDV for varying periods of time over their lifespan. No increase in the incidence of tumors was observed in the offspring of these mice, except in those offspring that had received additional lifetime ZDV exposure in whom the previously noted vaginal tumors once again were noted.

The relevance of these animal data to humans is unknown. An expert panel convened by the National Institutes of Health in January 1997 to review these data concluded that the proven benefit of ZDV in reducing the risk of perinatal transmission outweighed the hypothetical concerns of transplacental carcinogenesis raised by the rodent study. The panel also concluded that the information regarding the theoretical risk of transplacental carcinogenesis should be discussed with all HIV-infected pregnant women in the course of counseling them on the benefits and potential risks of antiretroviral therapy during pregnancy, and emphasized the need for careful long-term follow-up of all children exposed *in utero* to antiretroviral drugs. It is important to recognize that transplacental carcinogenicity studies have not been performed for any of the other available antiretroviral drugs, and no long-term or transplacental animal carcinogenicity studies of combinations of antiretroviral drugs have been performed.

All of the nucleoside analogue antiretroviral drugs except didanosine (ddI) are classified as FDA Pregnancy Category C (see footnote to Table 2 for definitions); ddI is classified as Category B. While all the nucleoside analogues cross the placenta in primates, in primate and placental perfusion studies ddI and ddC undergo significantly less placental transfer (fetal/maternal drug ratios of 0.3 to 0.5) than do ZDV, d4T and 3TC (fetal/maternal drug ratios >0.7).

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

There are 2 FDA-approved non-nucleoside reverse transcriptase inhibitors, nevirapine and delavirdine. A phase I study in the U.S. evaluated the safety and pharmacokinetics of nevirapine in 7 HIV-1-infected pregnant women and their infants. Nevirapine was administered as a single 200 mg oral dose at the onset of labor, and as a single dose of 2 mg per kg body weight at 2-3 days of age to their infants.(Mirochnick 1997) The drug was well-tolerated by the women, crossed the placenta and achieved neonatal blood concentrations equivalent to that in the mother. No short-term adverse effects were observed in mothers or neonates. Elimination of nevirapine in the pregnant women in this study was prolonged (mean half-life, 66 hours) compared to non-pregnant individuals (mean half-life, 45 hours following a single dose). Pharmacokinetic evaluation of chronic dosing with nevirapine beginning at 38 weeks gestation is under study but not yet available; no data are available regarding the safety and pharmacokinetics of chronic dosing with nevirapine beginning earlier in pregnancy. The half-life of nevirapine was prolonged in neonates (median half-life, 36.8 hours) compared to what is observed in older children (mean half-life, 24.8 hours following a single dose). A single dose of nevirapine at 2-3 days of age in neonates whose mothers received nevirapine during labor maintained levels associated with antiviral activity for the first week of life.(Mirochnick 1997) Based on these data, a phase III perinatal transmission prevention clinical trial sponsored by the PACTG will evaluate nevirapine administered as a 200 mg single dose to the woman during active labor and a single dose to the newborn at 2-3 days of age in combination with standard maternal antiretroviral therapy and ZDV chemoprophylaxis.

Delavirdine has not been studied in phase I pharmacokinetic and safety trials in pregnant women. In premarketing clinical studies outcomes of 7 unplanned pregnancies were reported. Three pregnancies resulted in ectopic pregnancies, and 3 resulted in healthy live births. One infant was born prematurely with a small muscular ventricular septal defect to a patient who received approximately 6 weeks of treatment with delavirdine and ZDV early in the course of pregnancy. Delavirdine is positive on at least one *in vitro* screening test for carcinogenic potential. Long-term and transplacental animal carcinogenicity studies are not available for either of these drugs at the present time. Both drugs are associated with impaired fertility in rodents when administered at high doses, and delavirdine is teratogenic in rodents when very high doses are administered during pregnancy (ventricular septal defects were observed at doses associated with severe maternal toxicity). Both nevirapine and delavirdine are classified as FDA Pregnancy Category C.

Protease Inhibitors

Although phase I studies of several protease inhibitors (indinavir, ritonavir and nelfinavir in combination with ZDV and 3TC) in pregnant infected women and their infants will soon start in the U.S., there are currently no data available regarding drug dosage, safety and tolerance of any of the protease inhibitors in pregnancy or in neonates. In mice, indinavir has significant placental passage, but in rabbits, little placental passage was observed. Ritonavir has been shown to have some placental passage in rats. Rodent data are not available on placental passage for saquinavir and nelfinavir, and transplacental passage of any of the protease inhibitors in humans is unknown.

Administration of indinavir to pregnant rodents has revealed no evidence of teratogenicity. However, treatment-related increases in the incidence of supernumerary and cervical ribs were observed in offspring of pregnant rodents receiving indinavir at doses comparable to those administered to humans. In pregnant rats receiving high doses of ritonavir that were associated with maternal toxicity, some developmental toxicity was observed in the offspring, including decreased fetal weight, delayed skeletal ossification, wavy ribs, enlarged fontanelles and cryptorchidism; however, in rabbits, only decreased fetal weight and viability was observed at maternally toxic doses. Rodent studies have not demonstrated embryotoxicity or teratogenicity with saquinavir or nelfinavir.

Indinavir is associated with infrequent side effects in adults (hyperbilirubinemia and renal stones) that could be problematic for the newborn if transplacental passage occurs and the drug is administered near to delivery. Due to the immature hepatic metabolic enzymes in neonates, the drug would likely have a prolonged half-life and possibly exacerbate the physiologic hyperbilirubinemia observed in neonates. Additionally, due to immature neonatal renal function and the inability of the neonate to voluntarily ensure adequate hydration, high drug concentrations and/or delayed elimination in the neonate could result in a higher risk for drug crystallization and renal stone development than observed in adults. These concerns are theoretical and such effects have not been reported; because the half-life of indinavir in adults is short, these concerns may only be relevant if drug is administered near the time of delivery. Saquinavir, ritonavir and nelfinavir are classified as FDA Pregnancy Category B; indinavir is classified as Category C.

The Food and Drug Administration has recently released a public health advisory regarding an association of new onset diabetes mellitus, hyperglycemia, exacerbation of existing diabetes mellitus and diabetic ketoacidosis with administration of any of the four currently available protease inhibitor antiretroviral drugs in HIV-infected patients.(FDA 97) Pregnancy is itself a risk factor for hyperglycemia, and it is unknown if the use of protease inhibitors will exacerbate the risk for pregnancy-associated hyperglycemia. Health care providers caring for infected pregnant women who are receiving protease inhibitor therapy should be aware of this possibility, and closely monitor glucose levels in their patients as well as instruct their patients in recognizing the early symptoms of hyperglycemia so they promptly seek health care if such symptoms develop.

Update on PACTG 076 Results and Other Studies Relevant to ZDV Chemoprophylaxis of Perinatal HIV-1 Transmission

Final results were reported in 1996 for all 419 infants enrolled in PACTG 076. The results are the same as those initially reported in 1994; the Kaplan-Meier estimated transmission rate in infants who received placebo was 22.6% compared to 7.6% within those who received ZDV, a 66% reduction in transmission risk.(Sperling 1996)

The mechanism by which ZDV reduced transmission in PACTG 076 has not been fully defined. The effect of ZDV on maternal HIV-1 RNA did not fully account for the observed efficacy of ZDV in reducing transmission, raising the possibility that pre-exposure prophylaxis of the fetus/infant is an important component of protection. If so, transplacental passage of antiretroviral drugs would be important for prevention of transmission. Additionally, in placental perfusion studies, ZDV has been shown to be metabolized into the active tri-phosphate within the placenta (Sandberg 1995, Qian 1994), and this could have provided additional protection against *in utero* transmission. This phenomenon may be unique to ZDV, as metabolism to the active tri-phosphate form within the placenta has not been observed in the other nucleoside analogues that have been studied in this fashion (ddI and ddC).(Dancis 1993, Sandberg 1994) Development of ZDV-resistant virus was not necessarily associated with failure to prevent transmission. In a preliminary evaluation of genotypic resistance in women in PACTG 076, ZDV-resistant virus was present at delivery in only one of 7 transmitting women who had received ZDV and had evaluable samples; this woman had ZDV resistant virus at study entry despite no prior ZDV experience.(Eastman 1997) Additionally, the one woman in whom virus developed ZDV genotypic resistance between entry and delivery in this evaluation did not transmit HIV-1 to her infant.

No increase in congenital abnormalities compared to the general population was seen in PACTG 076 or observed in evaluation of data from the Antiretroviral Pregnancy Registry.(AntiReg 1997) Follow-up data on uninfected infants from PACTG 076 to a median age of 3.9 years has not shown any differences in growth, neurodevelopment or immunologic status between infants born to mothers who received ZDV compared to those born to mothers who received placebo.(Connor1995) No malignancies have been observed in short-term (up to 6 years of age) follow-up over 734 infants from PACTG 076 and natural history studies who had *in utero* ZDV exposure.(Hanson 1997) However, follow-up is too limited at this time to provide a definitive assessment of carcinogenic risk with human exposure. Long-term follow-up continues to be recommended for all infants with *in utero* ZDV exposure (or *in utero* exposure to any of the antiretroviral drugs).

The effect of temporary administration of ZDV during pregnancy to reduce perinatal transmission on the induction of viral resistance to ZDV and long-term maternal health requires further evaluation. Preliminary data from an interim analysis of PACTG protocol 288 (a study following women enrolled in PACTG 076 through 3 years postpartum) indicate no significant differences at 18 months postpartum in CD4 lymphocyte count or clinical status between those women who received ZDV compared to those who received placebo.(Bardeguez 1997) Limited data on the development of genotypic ZDV resistance mutations (codons 70 and/or 215) in PACTG 076 are available from a subset of women receiving ZDV, including the majority of those with infected infants.(Eastman 1997) Virus from one of 36 ZDV-receiving women (3%) with paired isolates from entry and delivery developed a ZDV genotypic resistance mutation. However, the population of women in PACTG 076 had very low HIV-1 RNA copy number, and while the risk of inducing resistance with administration of ZDV chemoprophylaxis alone for several months during pregnancy was low in this substudy, it would likely be higher in a population of women with more advanced disease and higher levels of viral replication.

The efficacy of ZDV chemoprophylaxis for reducing transmission among populations of infected women with characteristics unlike those in PACTG 076 has been evaluated in another perinatal protocol (PACTG 185) as well as natural history studies. PACTG 185 evaluated the 3-part ZDV regimen combined with passive immunization with hyperimmune HIV-1 immunoglobulin (HIVIG), an immunoglobulin containing high levels of antibody to HIV-1, in infected pregnant women with advanced HIV-1 disease receiving antiretroviral therapy. Twenty-one percent of the women in this trial had CD4 count $<200/mm^3$ and 23% had received ZDV prior to the current pregnancy, many for prolonged periods of time. All women and infants in this study received the 3-part ZDV regimen, and were randomized to receive HIVIG vs standard intravenous immunoglobulin (IVIG). Because it was known that advanced disease and low CD4 count were associated with high risk for perinatal transmission, it was hypothesized that even with ZDV chemoprophylaxis, the perinatal transmission rate would be 11-15%. However, at the first interim analysis, the combined group transmission rate was only 4.8%, and did not significantly differ by duration of ZDV use or treatment arm (HIVIG vs IVIG).(PACTG 185 ExecSum 1997) Enrollment was halted because the unexpectedly low transmission rate resulted in an inability to answer the primary protocol question in a timely fashion. However, the results of the trial confirm the efficacy of ZDV observed in PACTG 076, and extend this efficacy to women with advanced disease, low CD4 count and prior ZDV therapy.

These data are also consistent with epidemiologic data from several natural history studies. In a study in Connecticut, 39% of women with CD4 count <200/mm^3 who did not receive ZDV therapy during pregnancy had infected infants compared to 4% of women with similar CD4 counts who received ZDV during pregnancy.(Simpson 1997) In North Carolina, perinatal HIV-1 transmission has declined over time from 21% in 1993 to 6% in early 1996; only 3% of women who received all three components of the ZDV regimen had infected infants.(Fiscus 1997) In a large U.S. prospective multicenter natural history cohort of 556 mother-infant pairs, perinatal transmission declined from 19% in infants born before March 1994, before the results of PACTG 076 were available, to 8% in infants born after March 1994; decline in transmission was observed regardless of maternal CD4 lymphocyte count, duration of membrane rupture, mode of delivery, gestational age, and illicit drug use.(Cooper 1996) In another multicenter U.S. cohort, perinatal transmission declined from 20% among 1,160 children born before March 1994 to 12% among 373 born afterwards.(Simonds 1996)

It is not known if all three parts of the ZDV chemoprophylaxis regimen are necessary for prevention of transmission. Several natural history studies suggest that the antenatal component of the regimen by itself may have efficacy similar to that observed in PACTG 076.(Boyer 94, Matheson 95, Simpson 97, Frenkel 97) Other data point toward the importance of the infant component of the regimen. In a retrospective case-control study of health care workers from the U.S., France and the United Kingdom with nosocomial exposure to HIV-1-infected blood, postexposure use of ZDV was significantly associated with reduced odds of contracting HIV-1 (adjusted odds ratio 0.2, 95% confidence interval, 0.1-0.6).(CDC 1996) However, in a study from North Carolina, the rate of infection in HIV-exposed infants who received only post-partum ZDV chemoprophylaxis was similar to that observed in infants who received no ZDV chemoprophylaxis.(Fiscus 1997)

At the present time, there are no clinical trials which demonstrate that antiretroviral drugs other than ZDV are effective in reducing perinatal transmission. Potent combination antiretroviral regimens have been shown to significantly suppress viral replication and improve clinical status in infected adults. However, the efficacy of ZDV exceeds the magnitude of reduction in plasma HIV-1 RNA copy number observed in PACTG 076. If pre-exposure prophylaxis of the infant is an important mechanism of prevention, it is possible that any antiretroviral drug with significant placental passage may be equally effective, although if antiretroviral activity within the placenta is important for protection, ZDV may be unique among the available nucleoside analogue drugs. While there are advantages of combination therapy for the woman's own health, further research is needed before it can be determined if there is an additional advantage to combination antiretroviral therapy for reducing perinatal transmission.

PERINATAL HIV-1 TRANSMISSION AND MATERNAL HIV-1 RNA COPY NUMBER

The clear correlation of HIV-1 RNA levels with disease progression risk in non-pregnant infected adults suggests that HIV-1 RNA should be monitored during pregnancy at least as often as recommended for non-pregnant individuals (eg., every 3 to 4 months or approximately once each trimester). Whether increased frequency of testing is needed during pregnancy is unclear and requires further study. Although there is no convincing data that pregnancy accelerates HIV-1 disease progression, longitudinal measurements of HIV-1 RNA levels during and after pregnancy have been evaluated in only one prospective cohort to date. In this cohort of 198 HIV-1-infected women, plasma HIV-1 RNA levels were higher at 6 months postpartum than antepartum in many women; this increase was observed in women who had received and not received ZDV during pregnancy, as well as in women who continued therapy postpartum.(Cao 1997)

Data on the correlation of viral load with risk of perinatal transmission have been conflicting, with some small studies suggesting an absolute correlation between HIV-1 RNA copy number and transmission risk.(Dickover 1996) However, in several larger studies while higher HIV-1 RNA levels were observed in transmitting women, there was large overlap in HIV-1 RNA copy number between transmitting and non-transmitting women, transmission was observed across the entire range of HIV-1 RNA levels (including in women with HIV-1 RNA copy number below the limit of detection of the assay), and the positive predictive value of RNA copy number for transmission was relatively low.(Mayaux 1997, Burchett 1996, Cao 1997, Thea 1997) In PACTG 076, there was a relationship between HIV-1 RNA copy number and transmission in women receiving placebo, but in ZDV-receiving women the relationship was markedly attenuated and no longer statistically significant.(Sperling 1996) No HIV-1 RNA threshold below which there was no risk of transmission was identified, and ZDV was effective in reducing transmission regardless of maternal HIV-1 RNA copy number.

While a general correlation between plasma and genital viral load has been described, women with undetectable plasma HIV-1 RNA levels in whom virus was detectable in the genital tract have been reported.(Rasheed 1996) If exposure to virus in the maternal genital tract during delivery is an important risk factor for perinatal transmission, then plasma HIV-1 RNA levels may not be a fully accurate indicator of risk.

Whether lowering maternal HIV-1 RNA copy number during pregnancy would reduce perinatal transmission risk requires more study. In a virologic study in 44 infected pregnant women, ZDV was effective in reducing transmission despite minimal effect on HIV-1 RNA levels, similar to what was observed in PACTG 076.(Melvin 1997) However, it is not known if a more potent antiretroviral regimen that more significantly suppresses viral replication would be associated with enhanced efficacy in reducing transmission risk over and above that observed with ZDV alone. At the present time, determination of HIV-1 copy number is important for decisions related to treatment. However, because ZDV benefit is observed regardless of maternal HIV-1 RNA level and because transmission may occur when HIV-1 RNA is not detectable, HIV-1 RNA should not be the determining factor in decisions regarding use of ZDV chemoprophylaxis against perinatal transmission.

GENERAL PRINCIPLES REGARDING USE OF ANTIRETROVIRALS IN PREGNANCY

Care of the HIV-1-infected pregnant woman should involve an ongoing collaboration between the HIV-specialist caring for the woman when she is not pregnant, her obstetrician, and the woman herself. Decisions regarding use of antiretroviral drugs during pregnancy should be made by the woman following discussion with her health care provider of the known and unknown benefits and risks of therapy. Initial evaluation of an infected pregnant woman should include an assessment of HIV-1 disease status and recommendations regarding antiretroviral treatment or alteration of her current antiretroviral regimen. This assessment should include evaluation of the degree of existing immunodeficiency determined by CD4 count; risk of disease progression determined by the level of plasma RNA; history of prior or current antiretroviral therapy; gestational age; and supportive care needs. For those women not currently receiving antiretroviral therapy, decision-making regarding initiation of therapy should be the same as for non-pregnant individuals, with the additional consideration of the potential impact of such therapy on the fetus and infant.(PanelRec 1997) Similarly, for women currently receiving antiretrovirals, decisions regarding alterations in therapy should use the same parameters as for non-pregnant individuals. Additionally, use of the 3-part ZDV chemoprophylaxis regimen, alone or in combination with other antiretrovirals, should be discussed with and offered to all infected pregnant women for the purpose of reducing perinatal transmission risk.

Decisions regarding the use and choice of antiretroviral drugs during pregnancy are complex and must balance a number of competing factors influencing risk and benefit. Discussion regarding use of antiretroviral drugs during pregnancy should include what is known and not known about the effects of such drugs on the fetus and newborn, including lack of long-term outcome data on use of any of the available antiretroviral drugs in pregnancy; what would be recommended in terms of treatment for her own health; and the efficacy of ZDV for reduction of perinatal transmission. These discussions should include what is known from preclinical and animal studies and available clinical information about use of the various antiretroviral agents during pregnancy. It is important to place the hypothetical risks of these drugs during pregnancy in perspective to the proven benefit of antiretroviral therapy for her own health and ZDV chemoprophylaxis for reducing the risk of HIV-1 transmission to her infant.

Discussion of treatment options should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. Decisions regarding use and choice of antiretroviral drugs in non-pregnant individuals are becoming increasingly complicated, as the standard of care moves toward simultaneous use of multiple antiretroviral drugs to suppress viral replication below detectable limits. These decisions are further complicated in pregnancy, as the long-term consequences of *in utero* exposure to antiretroviral drugs, alone or in combination, for the infant are unknown. A decision to not accept treatment with ZDV or other drugs should not result in punitive action or denial of care, nor should use of ZDV be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and therefore chooses to receive only ZDV during pregnancy to reduce the risk of perinatal transmission after receiving appropriate counseling.

A long-term treatment plan should be developed with the patient and the importance of adherence to any prescribed antiretroviral regimen discussed with her. Depending on individual circumstances, provision of support services, mental health services and drug abuse treatment may be required. Coordination of services between prenatal care providers and primary care and HIV specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential. Each plays an important role in assisting the woman with adherence to antiretroviral regimens and selection of the best option for her own health and for reduction of perinatal transmission.

General counseling should include information regarding what is known about risk factors for perinatal transmission. Some studies have shown an association of cigarette smoking, illicit drug use, and unprotected sexual intercourse with multiple partners during pregnancy with perinatal HIV-1 transmission risk (Burns 1994, Turner 1997, Rodriguez 1996, Bulterys 1997, Matheson 1996), and discontinuing these practices may have the added benefit of providing nonpharmacologic interventions that might reduce transmission risk. Additionally, the Public Health Service recommends that infected women in the U.S. should refrain from breastfeeding to avoid postnatal transmission of HIV-1 to their infants through breast milk (CDC 1985, CDC 1995), and these recommendations should not be altered for women receiving antiretroviral therapy. Passage of antiretroviral drugs into breast milk has been evaluated for only a few antiretroviral drugs: ZDV, 3TC and nevirapine can be detected in the breast milk of women receiving the drugs, and ddI, d4T, and indinavir can be detected in the breast milk of lactating rats receiving therapy. The efficacy of antiretroviral therapy for prevention of postnatal transmission of HIV-1 through breast milk and the toxicity of chronic antiretroviral exposure of the infant via breast milk are unknown.

It is strongly recommended that health care providers who are treating HIV-1-infected pregnant women and their newborns report cases of prenatal exposure to antiretroviral drugs (used either alone or in combination) to the Antiretroviral Pregnancy Registry. The registry is an epidemiologic project to collect observational, non-experimental data on antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity of these drugs in pregnancy. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project with an advisory committee of obstetric and pediatric practitioners, governmental staff from the CDC and NIH, and staff from pharmaceutical manufacturers. The registry does not use patient names, and birth outcome follow-up is obtained by registry staff from the reporting physician. Referrals should be directed to Antiretroviral Pregnancy Registry, Post Office Box 13398, Research Triangle Park, NC 27709-3398; telephone (919)-483-9437 or (800) 722-9292, ext. 39437; fax 919-315-8981.

RECOMMENDATIONS FOR ANTIRETROVIRAL CHEMOPROPHYLAXIS TO REDUCE PERINATAL HIV TRANSMISSION

The following recommendations for use of antiretroviral chemoprophylaxis to reduce the risk of perinatal transmission are based upon various circumstances that may be commonly encountered in clinical practice (Table 3), with relevant considerations highlighted in the subsequent discussion section. These scenarios present only recommendations and flexibility should be exercised according to the circumstances of the individual patient. In the 1994 recommendations, 6 clinical scenarios were delineated based on maternal CD4 count, gestational age and prior antiretroviral use. Because current data indicate that the PACTG 076 ZDV regimen is also effective for women with advanced disease, low CD4 count and prior ZDV therapy, clinical scenarios by CD4 count and prior ZDV use are not presented. Additionally, because current data indicate most transmission occurs near to or during delivery, it was felt that ZDV chemoprophylaxis should be recommended regardless of gestational age; thus, clinical scenarios by gestational age are also not presented.

Table 1 shows the ZDV dosage and regimen used in PACTG 076. The antenatal dosing regimen in PACTG 076 (100 mg orally five times daily) was selected based on standard ZDV dosage for adults at the time of the study. Recent reports from several laboratories have demonstrated that administration of ZDV three times a day will maintain intracellular ZDV tri-phosphate at levels comparable to that observed with more frequent dosing.(Rodman 1996; Barry 1996; Gambertoglio 1996) Additionally, comparable clinical response with twice daily dosing has been observed in some clinical trials.(Mulder 1994, Mannucci 1994, Cooper 1993) Thus, the current standard adult ZDV dosing regimen is 200 mg three times daily or 300 mg twice daily. Because the mechanism by which ZDV reduces perinatal transmission is not known, it cannot be known with certainty that these dosing regimens will have equivalent efficacy to that observed in PACTG 076. However, it would be anticipated that a two or three times daily regimen might be associated with enhanced maternal adherence over a five times daily regimen.

The recommended ZDV dosage for infants was derived from pharmacokinetic studies performed in term infants.(Boucher 1993) ZDV is primarily cleared through hepatic glucuronidation to an inactive metabolite. The glucuronidation metabolic enzyme system is immature in neonates, leading to prolonged ZDV half-life and clearance compared to older infants (ZDV half-life, 3.1 hours vs 1.9 hours, and clearance, 10.9 vs 19.0 mL per minute per kg body weight, respectively). Because premature infants have even greater immaturity in hepatic metabolic function than term infants, further prolongation in clearance may be expected. In a small pharmacokinetic study of 7 premature infants who were 28 to 33 weeks gestation and received a variety of ZDV dosing regimens, mean ZDV half-life was 6.3 hours and mean clearance was 2.8 mL per minute per kg body weight during the first 10 days of life.(Capparelli 1996) Appropriate ZDV dosing for premature infants has not been defined, but is being evaluated in a phase I clinical trial in premature infants less than 34 weeks gestation. The dosing regimen being studied is 1.5 mg per kg body weight orally or intravenously every 12 hours for the first 2 weeks of life; from 2 to 6 weeks of age, the dose is increased to 2 mg per kg body weight every 8 hours.

Because subtherapeutic dosing of antiretroviral drugs may be associated with enhancing the likelihood for the development of drug resistance, women who must temporarily discontinue therapy due to pregnancy-related hyperemesis should not reinstitute therapy until sufficient time has elapsed to assure that the drugs will be tolerated. In order to reduce the potential for emergence of resistance, if therapy requires temporary discontinuation for any reason during pregnancy, all drugs should be stopped and reintroduced simultaneously.

CLINICAL SCENARIOS

Scenario #1: HIV-infected pregnant women without prior antiretroviral therapy

Recommendation:

HIV-1 infected pregnant women must receive standard clinical, immunologic and virologic evaluation, and recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used in non-pregnant individuals, with consideration and discussion of the known and unknown risks and benefits of such therapy during pregnancy.(PanelRec 97) The 3-part ZDV chemoprophylaxis regimen should be recommended for all HIV-infected pregnant women to reduce the risk of perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV infection should be discussed, recommended for infected women whose clinical, immunologic and virologic status indicates the need for treatment, and offered to other women, although in the latter circumstance it is not known if the combination of antenatal ZDV chemoprophylaxis with other antiretroviral drugs will provide additional benefit or risks for the infant. Women who are in the first trimester of pregnancy may wish to consider delaying initiation of therapy until after 10 to 12 weeks gestation.

Discussion:

The only drug that has been shown to reduce the risk of perinatal HIV-1 transmission is ZDV when administered in the 3-part PACTG 076 regimen; this regimen was shown to reduce transmission risk by approximately 70%. The mechanism by which ZDV reduced transmission is not known, and there are insufficient data available at present to justify the substitution of any antiretroviral drug other than ZDV for the purpose of reducing perinatal transmission. Therefore, if combination antiretroviral therapy is initiated during pregnancy, it is recommended that ZDV be included as a component of antenatal therapy and the intrapartum and newborn ZDV parts of the chemoprophylactic regimen should be recommended for the specific purpose of reducing perinatal transmission.

Women should be counseled that combination therapy may have significant benefit for their own health but is of unknown benefit to the fetus. Potent combination antiretroviral regimens may be shown in the future to provide enhanced protection against perinatal transmission, but this benefit is not yet proven. Decisions regarding the use and choice of an antiretroviral regimen will need to be individualized based on discussion with the woman about her risk for disease progression and the risks and benefits of delaying initiation of therapy; potential drug toxicities and interactions with other drugs; the need for adherence to the prescribed drug schedule; and preclinical, animal and clinical data relevant to use of the currently available antiretrovirals during pregnancy.

Because the period of organogenesis when the embryo is most susceptible to potential teratogenic effects of drugs is the first 10 weeks of gestation and the risks of antiretroviral therapy during that period are unknown, women who are in the first trimester of pregnancy may wish to consider delaying initiation of therapy until after 10 to 12 weeks gestation. This decision should be carefully considered and discussed between the health care provider and the patient, including an assessment of the woman's health status and the benefits and risks of delaying initiation of therapy for several weeks.

Women for whom initiation of antiretroviral therapy for the treatment of their HIV infection would be considered optional (eg. high CD4 count and low or undetectable RNA copy number) should have the potential benefits of standard combination therapy discussed with them and standard therapy, including the 3-part ZDV chemoprophylaxis regimen, offered to them. Some women may wish to restrict their exposure to antiretroviral drugs during pregnancy but still wish to reduce the risk of transmitting HIV-1 to their infant; the 3-part ZDV chemoprophylaxis regimen should be recommended in this situation. In these circumstances, the development of resistance should be minimized by the limited viral replication in the patient and the time-limited exposure to ZDV.

Because ZDV alone does not suppress HIV replication to undetectable levels, there are theoretical concerns that use of ZDV chemoprophylaxis alone might select for ZDV resistant viral variants which might limit future ability to favorably respond to combination antiretroviral regimens that include ZDV. There are currently insufficient data to determine if such use would have adverse consequences for the woman postpartum. In some adult combination antiretroviral clinical trials, patients with previous ZDV therapy experienced less benefit from combination therapy than those who were antiretroviral naive.(Delta 1996, Hammer 1996, Saravolatz 1996) However, the median duration of prior ZDV in these studies was 12 to 20 months and enrolled patients had more advanced disease and lower CD4 counts than the population of women enrolled in PACTG 076 or for whom initiation of therapy would be considered optional. In one study, patients with less than 12 months of ZDV responded as favorably to combination therapy as did those without prior ZDV therapy.(Saravolatz 1996) In PACTG 076, the median duration of ZDV therapy was 11 weeks, and the maximal duration of ZDV begun at 14 weeks gestation would be 6.5 months for a full-term pregnancy.

However, for women initiating therapy who have more advanced disease, concerns about development of resistance with use of ZDV alone as chemoprophylaxis during pregnancy would be greater. Factors that predict more rapid development of ZDV resistance include more advanced HIV-1 disease, low CD4 count, high HIV-1 RNA copy number, and possibly syncytium-inducing viral phenotype.(Kuritzkes 1996, Japour 1995) Therefore, women with advanced disease, low CD4 count or high RNA copy number should be counseled that therapy with a combination antiretroviral regimen that includes ZDV for reducing transmission risk would be more optimal for their own health than use of ZDV chemoprophylaxis alone.

Scenario #2: HIV-infected women receiving antiretroviral therapy during the current pregnancy

Recommendation:

HIV-1 infected women receiving antiretroviral therapy in whom pregnancy is identified after the first trimester should continue therapy. For women receiving antiretroviral therapy in whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of resistance. If the current therapeutic regimen does not contain ZDV, the addition of ZDV or substitution of ZDV for another nucleoside analogue antiretroviral is recommended after 14 weeks gestation. Intrapartum and newborn ZDV administration is recommended regardless of the antepartum antiretroviral regimen.

Discussion:

Women who require antiretroviral treatment for their HIV infection should continue treatment during pregnancy. Discontinuation of therapy could lead to rebound in viral load, which theoretically could result in decline in immune status and/or disease progression, all of which might have adverse consequences for the fetus as well as the woman. Because the efficacy of non-ZDV containing antiretroviral regimens for reduction of perinatal transmission is unknown, it is recommended that ZDV be a component of the antenatal antiretroviral treatment regimen after 14 weeks gestation, and that intrapartum and newborn ZDV be administered. If a woman does not receive ZDV as a component of her antepartum antiretroviral regimen (eg. because of prior history of ZDV-related severe toxicity or personal choice), intrapartum and newborn ZDV should continue to be recommended.

Some women receiving antiretroviral therapy may recognize their pregnancy early in gestation, and concern for potential teratogenicity may lead some to consider temporarily stopping antiretroviral treatment until after the first trimester. There are insufficient data to support or refute the teratogenic risk of antiretroviral drugs when administered during the first 10 weeks of gestation. The decision to continue therapy during the first trimester should be carefully considered and discussed between the clinician and the woman. Considerations include gestational age of the pregnancy, the woman's clinical, immunologic and virologic status, and what is known and not known about the potential effects of the antiretroviral drugs on the fetus. If antiretroviral therapy is discontinued during the first trimester, all agents should be stopped and restarted in the second trimester simultaneously to avoid the development of resistance. There are currently no data to address whether transient discontinuation of therapy in this manner would be harmful for the woman and/or fetus.

The impact of prior antiretroviral exposure on the efficacy of ZDV chemoprophylaxis is unclear. Data from PACTG 185 indicate that duration of prior ZDV therapy in women with advanced HIV-1 disease, many of whom received prolonged ZDV prior to pregnancy, did not appear to be associated with diminished ZDV efficacy for reduction of transmission: perinatal transmission rates were similar among women who first initiated ZDV during pregnancy and women who had received ZDV prior to pregnancy. Thus at the present time, a history of ZDV therapy prior to the current pregnancy should not limit recommendations for administration of ZDV chemoprophylaxis to reduce perinatal transmission.

Some experts might consider administration of ZDV in combination with other antiretroviral drugs to newborns of women with a history of prior antiretroviral therapy, particularly in situations where the woman is infected with HIV-1 with documented high-level ZDV resistance, had disease progression while receiving ZDV, or had extensive prior ZDV monotherapy. However, the efficacy of this approach is not known. The appropriate dose and short and long-term safety for most antiretroviral agents other than ZDV are not defined for neonates. Phase I studies have shown that the half-lives of ZDV, 3TC and nevirapine are prolonged during the neonatal period due to immature liver metabolism and renal function, requiring specific dosing adjustments when these antiretrovirals are given to neonates. Data on the pharmacokinetics of other antiretroviral drugs in neonates are not yet available, although phase I neonatal studies of a number of other antiretrovirals are ongoing. The infected woman should be counseled regarding the postulated benefit of combination antiretroviral drugs in the neonate and the potential risks, what is known about appropriate dosing of the drugs in newborn infants, and that use of additional antiretroviral drugs for newborn prophylaxis is of unknown efficacy for reducing perinatal transmission risk.

Scenario #3: HIV-infected women in labor who have had no prior therapy

Recommendation:

Administration of intrapartum intravenous ZDV should be recommended along with the 6 week newborn ZDV regimen. In the immediate postpartum period, the woman should have appropriate assessments (eg., CD4 count, HIV-1 RNA copy number) to determine if antiretroviral therapy is recommended for her own health.

Discussion:

Intrapartum ZDV will not prevent the portion of perinatal transmission that occurs prior to labor. Therefore, the efficacy of an intrapartum/newborn antiretroviral regimen in reducing perinatal transmission is likely to be less than the efficacy observed in PACTG 076. However, increasing data indicate that a majority of perinatal transmission occurs near to or during birth. Additionally, the efficacy of ZDV in reducing perinatal transmission is not primarily related to treatment-induced reduction in maternal HIV-1 RNA copy number. This implies that the presence of systemic antiretroviral drug levels in the neonate just prior to, during and for a period following birth may be a critical component for reducing transmission.

There are minimal data to address the efficacy of a regimen that lacks the antenatal ZDV component. An epidemiologic study from North Carolina compared perinatal transmission rates from mother-infant pairs who received different parts of the ZDV chemoprophylactic regimen.(Fiscus 1997) Among those who received all 3 components, 6 of 188 infants were infected (3%). While the numbers were small, only one of 16 infants (6%) were infected among those who received intrapartum and newborn ZDV.

ZDV readily crosses the placenta. Administration of the intravenous ZDV loading dose followed by continuous ZDV infusion during labor to the woman will provide ZDV levels in the newborn during passage through the birth canal that are nearly equivalent to maternal ZDV levels. The initial intravenous ZDV loading dose assures rapid attainment of virucidal ZDV levels in the woman and her infant, and the continuous ZDV infusion assures stable drug levels in the infant during the birth process regardless of the duration of labor. A study is currently ongoing in the U.S. to evaluate if oral dosing of ZDV during labor in a regimen of 300 mg orally every 3 hours would provide equivalent infant drug exposure to intravenous ZDV administration. Until these data are available, oral intrapartum administration of ZDV cannot be assumed to be equivalent to the intravenous intrapartum ZDV.

ZDV administered both during the intrapartum period and to the newborn provides both pre-and post-exposure prophylaxis to the infant. Post-exposure prophylaxis recommendations have been made for nosocomial exposure of health care workers to HIV-1-infected blood.(CDC 1996) In such cases, it is recommended that ZDV be administered as soon after exposure as possible, with the addition of 3TC in most cases to provide increased antiretroviral activity and presumed activity against ZDV-resistant HIV-1 strains. The addition of a protease inhibitor is recommended for particularly high-risk exposures. In situations in which the antenatal component of the three-part ZDV regimen has not been received, some clinicians might consider administration of ZDV in combination with other antiretroviral drugs, analogous to nosocomial post-exposure prophylaxis. However, there are no data to address whether the addition of other antiretroviral drugs to ZDV increase the effectiveness of post-exposure prophylaxis in this situation or for nosocomial exposure. Any decision to use combination antiretroviral prophylaxis in the newborn must be accompanied by a discussion with the woman of potential benefits and risks and that there currently are no data to address the efficacy and safety of this approach.

Scenario #4: Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum

Recommendation:

The 6 week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn; ZDV should be initiated as soon as possible after birth, preferably within 12-24 hours after birth. Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother has known or suspected ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission is unknown and appropriate dosing regimens for neonates are incompletely defined. In the immediate postpartum period, the woman should undergo appropriate assessments (eg., CD4 count, HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health.

Discussion:

Definitive data are not available to address whether ZDV administered solely during the neonatal period would reduce the risk of perinatal transmission. However, data from a case-control study of post-exposure prophylaxis of health care workers who had nosocomial percutaneous exposure to blood from HIV-1-infected individuals indicate that ZDV administration was associated with a 79% reduction in the risk for HIV-1 seroconversion following exposure.(CDC 1995) Post-exposure prophylaxis has also been shown to prevent retroviral infection in some animal studies.(Van Rompay 1995, Tsai 1995, Bottiger 1997)

The interval for which benefit may be gained from post-exposure prophylaxis is undefined, but data from animal studies indicate that the longer the delay in institution of prophylaxis, the less likely prevention will be observed. In most animal studies, antiretroviral prophylaxis initiated after 24-36 hours is usually not effective for preventing infection, although later administration has been associated with decreased viremia in ultimately infected animals in some cases.(VanRompay 1995, Bottiger 1997, Tsai 1995) In the feline leukemia virus cat model, ZDV treatment initiated within the first 4 days after viral challenge afforded protection, while treatment initiated one week postexposure did not prevent infection.(Mathes 1992) The relevance of the animal studies to prevention of perinatal transmission in humans is unknown. HIV-1 infection is established in the majority of infected infants by 1 to 2 weeks of age. In a study of 271 infected infants, HIV-1 DNA polymerase chain reaction (PCR) was positive in 38% of infected infants tested within 48 hours of birth. No major change in diagnostic sensitivity was observed over the first week of life, but detection rose rapidly during the second week of life, reaching 93% by 14 days of age.(Dunn 1995) Therefore, it would be unlikely that initiation of post-exposure prophylaxis after 14 days of age would have efficacy in preventing transmission, as infection would already be established in most children.

When neither the antenatal and intrapartum parts of the three-part ZDV regimen are received by the mother, administration of antiretroviral drugs to the newborn will provide chemoprophylaxis only after HIV-1 exposure has already occurred. Some clinicians view this situation as analogous to nosocomial post-exposure prophylaxis, and may wish to provide ZDV in combination with one or more other antiretroviral agents. Such a decision must be accompanied by a discussion with the woman of potential benefits and risks of this approach and lack of data to address its efficacy and safety.

RECOMMENDATIONS FOR MONITORING OF WOMEN AND THEIR INFANTS

Pregnant woman and fetus:

HIV-1-infected pregnant women should be monitored in the same fashion that nonpregnant individuals are monitored. This should include measurement of CD4 lymphocyte count and HIV-1 RNA levels approximately every trimester (every 3 to 4 months) to determine need for antiretroviral therapy of maternal HIV-1 disease or alterations in such therapy, and/or initiation of prophylaxis against *Pneumocystis carinii* pneumonia. Some studies have found that changes in absolute CD4 count during pregnancy may reflect the physiologic changes of pregnancy on hemodynamic parameters and blood volume as opposed to a longterm influence of pregnancy upon CD4 count; CD4 percent appears to be more stable and may be a more accurate reflection of immune status during pregnancy.(Miotti 1992, Tuomala 1997) Long-range plans should be developed with the woman regarding continuity of medical care and antiretroviral therapy for her own health after she delivers her infant.

Monitoring for potential complications of antiretroviral administration during pregnancy should take into account what is known about the side effects of the drugs the woman is receiving. For example, routine hematologic and liver enzyme monitoring is recommended for women receiving ZDV, and women receiving protease inhibitors should be monitored for the development of hyperglycemia. Because there is less experience with use of combination antiretroviral regimens during pregnancy, more intensive monitoring may be warranted for women receiving drugs other than or in addition to ZDV.

Antepartum fetal monitoring for women who receive only ZDV chemoprophylaxis should be performed as clinically indicated, as the available data do not indicate that ZDV use in pregnancy is associated with increased risk for fetal complications. However, much less is known about the effect of combination antiretroviral therapy during pregnancy on the fetus. More intensive monitoring should be considered, including assessment of fetal anatomy with a level II ultrasound and continued assessment of fetal growth and well-being during the third trimester.

Neonate:

A complete blood count and differential should be performed as a baseline evaluation prior to administration of ZDV. Anemia has been the primary complication of the 6 week ZDV regimen in the neonate, thus at a minimum, repeat measurement of hemoglobin is required at the completion of the 6 week ZDV regimen; repeat measurement may be performed at 12 weeks of age, by which any ZDV-related hematologic toxicity should be resolved. Infants who have anemia at birth or who are premature warrant more intensive monitoring.

There is little experience with potential toxicities in infants whose mothers have received combination antiretroviral therapy. More intensive monitoring of hematologic and serum chemistry measurements during the first few weeks of life would be advised in these infants.

All infants born to HIV-1-infected women should be placed on prophylaxis to prevent *Pneumocystis carinii* pneumonia at 6 weeks of age, following completion of the ZDV prophylaxis regimen.(CDC 1995) Monitoring and diagnostic evaluation of HIV-1-exposed infants should follow current standards of care. The available data do not indicate any delay in HIV-1 diagnosis in infants who have received the ZDV regimen.(Connor 1994, Kovacs 1995) However, the effect of combination antiretroviral therapy in the mother and/or newborn on the sensitivity of infant virologic diagnostic testing is unknown. Infants with negative virologic tests during the first 6 weeks of life should have diagnostic evaluation repeated after completion of the neonatal antiretroviral prophylaxis regimen.

Postpartum Follow-Up of Women:

Comprehensive care and support services are required for women infected with HIV-1 and their families. Components of comprehensive care include the full range of medical and supportive care services including primary, obstetric and HIV specialty care, family planning, mental health services and drug abuse treatment; coordination of care through case management for the woman, her children and other family members. Support services include case management, childcare, respite care, assistance with basic life needs such as housing, food, and transportation, as well as legal and advocacy services. This care should begin prior to pregnancy, with continuity of care ensured throughout pregnancy and postpartum.

Maternal medical services during the postpartum period must be coordinated between obstetric and HIV-specialist health care providers. Continuity of antiretroviral treatment when therapy is required for treatment of the woman's HIV infection is especially critical and must be ensured. All women should have linkage with comprehensive health care services that continues after pregnancy for their own medical care and for assistance with family planning and contraception.

Data from PACTG Protocols 076 and 288 do not indicate adverse effects through 18 months postpartum among women who received ZDV during pregnancy; however, continued clinical, immunologic and virologic follow-up of these women is ongoing. Women who have received only ZDV chemoprophylaxis during pregnancy should receive appropriate evaluation to determine the need for antiretroviral therapy in the postpartum period.

Long-Term Follow-Up of Infants:

Data remain insufficient to address the effect that exposure to ZDV or other antiretroviral agents *in utero* might have on long-term risk for neoplasia or organ system toxicities in children. Data from follow-up of PACTG 076 infants through 18 to 36 months of age do not indicate any differences in immunologic, neurologic and growth parameters between infants who were exposed to the ZDV regimen compared to placebo; continued intensive follow-up through PACTG 219 is ongoing. PACTG 219 will also provide intensive follow-up for infants born to women who receive other antiretroviral drugs as part of PACTG perinatal protocols, so some data regarding follow-up of exposure to other antiretroviral agents alone or in combination will be available in the future.

Innovative methods are needed to provide follow-up to infants with *in utero* exposure to ZDV or any other antiretrovirals outside of PACTG protocols. Information regarding such exposure should be part of the ongoing medical record of the child, particularly for uninfected children. Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding potential for carcinogenicity of the nucleoside analogue antiretroviral drugs. Long-term follow-up should include at least yearly physical examination of all antiretroviral-exposed children, and for older adolescent females, gynecologic evaluation with pap smears.

On a population basis, HIV-1 surveillance databases from states that require HIV-1 reporting provide an opportunity to collect information on *in utero* antiretroviral exposure. To the extent permitted by federal law and regulations, these confidential registries can be used to compare to birth defect and cancer registries to look for potential adverse outcomes.

Future Research Needs

An increasing number of HIV-1-infected women will be receiving antiretroviral therapy for their own health during pregnancy. Preclinical evaluations of antiretroviral drugs for potential pregnancy- and fetal-related toxicities should be completed for all current and new antiretroviral drugs. More data are needed regarding the safety and pharmacokinetics of antiretroviral drugs during pregnancy and in the neonate, particularly when used in combination regimens. Results from a number of phase I studies will be available in the next year which will assist in delineating appropriate dosing and provide data on short-term safety of these drugs in pregnant women and infants. However, the long-term consequences of *in utero* antiretroviral exposure for the infant are unknown, and mechanisms must be developed to gather information about the long-term outcome for exposed infants. Innovative methods are needed to enable identification and follow-up of populations of children with *in utero* antiretroviral exposure.

Additional studies are needed to determine the long-term consequences of transient use of ZDV chemoprophylaxis during pregnancy for women who do not desire to receive combination therapy antenatally, including the risk for development of ZDV-resistance.

While there are theoretical reasons to believe that more potent antiretroviral combination regimens that dramatically diminish viral load may also prevent perinatal transmission, there are currently no data to address this hypothesis. The efficacy of combination antiretroviral therapy specifically to decrease the risk of perinatal HIV-1 transmission needs to be evaluated in ongoing and future perinatal clinical trials. Additionally, epidemiologic studies and clinical trials are needed to delineate the relative efficacy of the various components of the 3-part ZDV chemoprophylactic regimen. Improved understanding of the factors associated with perinatal transmission despite ZDV chemoprophylaxis is needed in order to develop alternative effective regimens. Because of the dramatic decline in perinatal HIV-1 transmission with widespread implementation of ZDV chemoprophylaxis, the conduct of such epidemiologic studies and clinical trials requires an international collaborative effort.

Additionally, regimens that are more feasible for implementation in the developing world are urgently needed. The 3-part ZDV chemoprophylactic regimen is complex and may not be a feasible option for many developing countries: most pregnant women show up in health care systems only around the time of delivery; widespread safe administration of intravenous ZDV infusions during labor may not be possible; and the cost of the regimen may be prohibitive and many times greater than the per capita health expenditures for the country. There are several ongoing studies in developing countries that are evaluating the efficacy of more practical, abbreviated modifications of the ZDV regimen. Additionally, a number of non-antiretroviral interventions are also under study. Results of these studies will be available in the next few years.

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Table 1. PACTG 076 ZDV Regimen

Antepartum	Oral administration of 100 mg ZDV five times daily, initiated at 14-34 weeks gestation and continued throughout the pregnancy.
Intrapartum	During labor, intravenous administration of ZDV in a 1-hour loading dose of 2 mg per kg of body weight, followed by a continuous infusion of 1 mg per kg of body weight per hour until delivery.
Postpartum	Oral administration of ZDV to the newborn (ZDV syrup at 2 mg per kg body weight per dose every 6 hours) for the first 6 weeks of life, beginning at 8-12 hours after birth (Note: intravenous dosage for infants who cannot tolerate oral intake is 1.5 mg per kg body weight intravenously every 6 hours).

Table 2. Preclinical and Clinical Data Relevant to Use of Antiretrovirals in Pregnancy[1]

Antiretroviral Drug	FDA Pregnan-cy Category*	Placental Passage [Newborn:Maternal Drug Ratio]	Long-Term Animal Carcinogenicity Studies
Nucleoside Analogue Reverse Transcriptase Inhibitors			
Zidovudine (ZDV)	C	Yes (human) [0.85]	Positive (rodent, noninvasive vaginal epithelial tumors)
Zalcitabine (ddC)	C	Yes (rhesus) [0.30-0.50]	Positive (rodent, thymic lymphomas)
Didanosine (ddI)	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)
Stavudine (d4T)	C	Yes (rhesus) [0.76]	Not completed
Lamivudine (3TC)	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)
Non-Nucleoside Reverse Transcriptase Inhibitors			
Nevirapine	C	Yes (human) [~1.0]	Not completed
Delavirdine	C	Unknown	Not completed

Antiretroviral Drug	FDA Pregnan-cy Category*	Placental Passage [Newborn:Maternal Drug Ratio]	Long-Term Animal Carcinogenicity Studies
Protease Inhibitors			
Indinavir	C	Yes (rats) "Significant" in rats, but low in rabbits	Not completed
Ritonavir	B	Yes (rats) [mid-term fetus, 1.15; late-term fetus, 0.15-0.64]	Not completed
Saquinavir	B	Unknown	Not completed
Nelfinavir	B	Unknown	Not completed

* FDA Pregnancy Categories are:

A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters);

B - Animal reproduction studies fail to demonstrate a risk to the fetus and adequate but well-controlled studies of pregnant women have not been conducted;

C - Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus;

D - Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks;

X - Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

[1] Information included in these guidelines may not represent FDA approval or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

Table 3. Summary: Clinical Situations and Recommendations for Use of Antiretroviral Drugs to Reduce Perinatal HIV Transmission

Clinical Scenario	Recommendation*
SCENARIO #1: HIV-infected pregnant women without prior antiretroviral therapy.	HIV-1 infected pregnant women must receive standard clinical, immunologic and virologic evaluation, and recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used in non-pregnant individuals, with consideration and discussion of the known and unknown risks and benefits of such therapy during pregnancy. The 3-part ZDV chemoprophylaxis regimen should be recommended for all HIV-infected pregnant women to reduce the risk of perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV infection should be discussed, recommended for infected women whose clinical, immunologic and virologic status indicates the need for treatment, and offered to other women, although in the latter circumstance it is not known if the combination of antenatal ZDV chemoprophylaxis with other antiretroviral drugs will provide additional benefit or risks for the infant. Women who are in the first trimester of pregnancy may wish to consider delaying initiation of therapy until after 10 to 12 weeks gestation.
SCENARIO #2: HIV-infected women receiving antiretroviral therapy during the current pregnancy.	HIV-1 infected women receiving antiretroviral therapy in whom pregnancy is identified after the first trimester should continue therapy. For women receiving antiretroviral therapy in whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of resistance. If the current therapeutic regimen does not contain ZDV, the addition of ZDV or substitution of ZDV for another nucleoside analogue antiretroviral is recommended after 14 weeks gestation. Intrapartum and newborn ZDV administration is recommended regardless of the antepartum antiretroviral regimen.

Clinical Scenario	Recommendation
SCENARIO #3: HIV-infected women in labor who have had no prior therapy.	Administration of intrapartum intravenous ZDV should be recommended along with the 6 week newborn ZDV regimen. In the immediate postpartum period, the woman should have appropriate assessments (eg., CD4 count, HIV-1 RNA copy number) to determine if antiretroviral therapy is recommended for her own health.
SCENARIO #4: Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum.	The 6 week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. ZDV should be initiated as soon as possible after birth, preferably within 12-24 hours after birth. Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother has known or suspected ZDV-resistant virus. However, the efficacy of this approach is unknown for prevention of transmission is unknown and appropriate dosing regimen for neonates are incompletely defined. In the immediate postpartum period, the woman should undergo appropriate assessments (eg., CD4 count, HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health.

* General note: Discussion of treatment options and recommendations should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. A decision to not accept treatment with ZDV or other drugs should not result in punitive action or denial of care, nor should use of ZDV be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and therefore chooses to receive only ZDV during pregnancy to reduce the risk of perinatal transmission.